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Cefiderocol Remains Highly Active Against Carbapenemase-Producing Enterobacterales

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BACKGROUND

- Infections with carbapenem-resistant Enterobacterales are associated with poor outcomes and high mortality, necessitating the use of appropriate antibiotic treatment.
- Cefiderocol is a siderophore conjugated cephalosporin with good stability against all classes of β-lactamases and is approved in the United States for the treatment of adult patients with complicated urinary tract infections and hospital-acquired/ventilator-associated bacterial pneumonia caused by susceptible Gram-negative pathogens and in Europe for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.
- In this study, the *in vitro* activity of cefiderocol and comparator agents was assessed against carbapenemase-carrying Enterobacterales that were collected during 2020–2022 in Europe and the USA as part of the SENTRY Antimicrobial Surveillance Program.

METHODS

- 24,084 Enterobacterales were collected and 587 (2.4%) that were non-susceptible to meropenem and/or imipenem by Clinical and Laboratory Standards Institute (CLSI) breakpoints were subjected to whole-genome sequencing to determine their carbapenemase content.
- Minimum inhibitory concentrations (MICs) were determined according to CLSI guidelines using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents, and iron-depleted CAMHB for cefiderocol.
- Susceptibility was assessed according to 2024 CLSI, US Food and Drug Administration (FDA), and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.

RESULTS

- 474 of 587 meropenem- and/or imipenem-non-susceptible isolates (80.7%) carried carbapenemase genes; the majority of them were *Klebsiella pneumoniae* (**Figure 1**).
- Genes for KPC enzymes were most frequently encountered, followed by OXA-48-like and NDM (**Figure 2**).
- Cefiderocol was highly active against isolates carrying carbapenemase genes (**Figure 3A**), whereas activity of β-lactam–β-lactamase inhibitor combinations depended on the carbapenemase detected (**Figure 3A**), with the exception of aztreonam-avibactam (**Figure 3B**).
- When applying EUCAST breakpoints (i.e., 2 mg/L), susceptibility to cefiderocol was lower because of the number of isolates with cefiderocol MIC values of 4 mg/L (**Table 1**), but cefiderocol, together with aztreonam-avibactam, remained one of the most active β-lactams, especially against isolates carrying metallo-β-lactamase genes (**Figure 3B**).

Figure 1. Distribution of meropenem- and/or imipenem-non-susceptible Enterobacterales species carrying carbapenemases

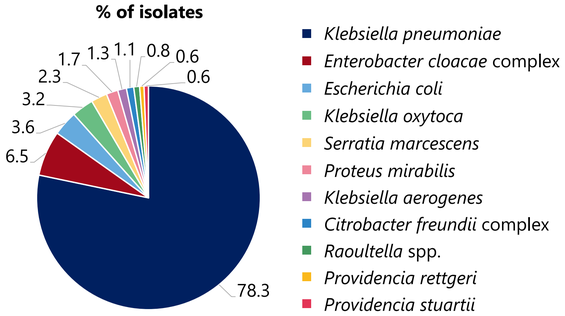
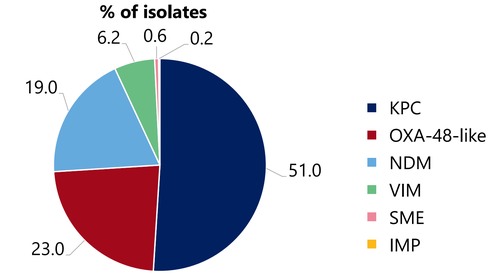


Figure 2. The distribution of carbapenemases in carbapenemase-producing meropenem- and/or imipenem-non-susceptible Enterobacterales



KPC, *Klebsiella pneumoniae carbapenemase*; IMP, imipenemase MBL; MBL, metallo-β-lactamase; NDM, New Delhi MBL; OXA, oxacillinase; SME, *Serratia marcescens* enzyme; VIM, Verona integron-encoded MBL.

CONCLUSIONS

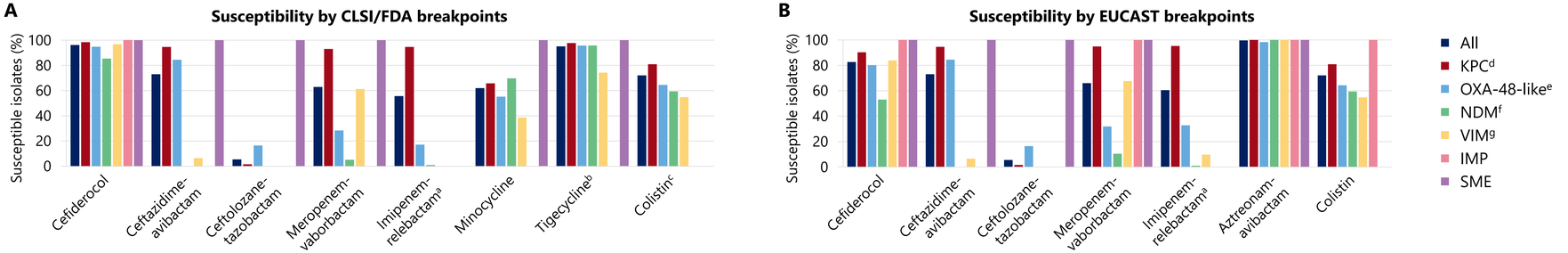
- Cefiderocol is active against Enterobacterales isolates carrying carbapenemase genes, regardless of the carbapenemase detected. In contrast, β-lactam–β-lactamase inhibitor combinations, with the exception of aztreonam-avibactam, showed variable activity.
- Cefiderocol should be considered as a treatment option when carbapenemase-producing Enterobacterales are encountered.

Table 1. Cefiderocol MIC distribution for carbapenemase-producing meropenem- and/or imipenem-non-susceptible Enterobacterales

	Number (%) of isolates with cefiderocol MIC of														
Carbapenemase	**0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	***2***	***4***	**8**	**16**	**32**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**
All	3 (0.6)	5 (1.1)	15 (3.2)	21 (4.4)	43 (9.1)	62 (13.1)	79 (16.7)	69 (14.6)	95 (20.0)	64 (13.5)	17 (3.6)	0 (0)	1 (0.2)	1	4
KPC	2 (0.8)	2 (0.8)	9 (3.5)	11 (4.3)	28 (10.9)	47 (18.3)	51 (19.8)	37 (14.4)	45 (17.5)	21 (8.2)	3 (1.2)	0 (0)	1 (0.4)	0.5	2
OXA-48-like	1 (0.9)	3 (2.6)	4 (3.4)	6 (5.2)	12 (10.3)	12 (10.3)	18 (15.5)	16 (13.8)	21 (18.1)	17 (14.7)	6 (5.2)			1	4
NDM				1 (1.0)	1 (1.0)	1 (1.0)	5 (5.2)	14 (14.6)	29 (30.2)	31 (32.3)	14 (14.6)			2	8
VIM			1 (3.2)	2 (6.5)	3 (9.7)	2 (6.5)	10 (32.3)	3 (9.7)	5 (16.1)	4 (12.9)	1 (3.2)			0.5	4
IMP									1 (100)						
SME			1 (33.3)	1 (33.3)	0 (0)	0 (0)	1 (33.3)							0.06	

EUCAST (light pink) and CLSI (dark pink) susceptibility breakpoints are highlighted by underlined letters in italics, respectively.

Figure 3. Activity of cefiderocol and comparator agents against Enterobacterales carrying carbapenemases, according to available CLSI/FDA (A) and EUCAST (B) breakpoints



[a]All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella, Proteus,* and *Providencia* species, and EUCAST excludes Morganellaceae. [b]FDA breakpoints only. [c]% Intermediate is shown. [d]Includes 9 KPC-and VIM-producing isolates, and 3 KPC- and NDM-producing isolates. [e]Includes 17 OXA- and NDM-producing isolates, and 1 OXA- and VIM-producing isolate. [f]Includes 17 NDM- and OXA-48-like-producing isolates, and 3 NDM- and KPC-producing isolates. [g]Includes 9 VIM- and KPC-producing isolates, 1 VIM- and OXA-producing isolate, and 5 double VIM-producing isolates.

Conflict of interest. BD, STN, JJB, CL, MT, YY are employees of Shionogi. This study was funded by Shionogi & Co., Ltd., Osaka, Japan.